The Use of Physics-Based Modeling to Better Design Drug-Device Interface

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Presentation Outline

- Physics-based modeling in pharmaceutical industry
- Pulmonary drug delivery
- Inhaler design
  - Aerosol physics
  - Numerical models for inhaler design
  - In Vitro-in Vivo correlation
- Case studies on optimization of Formulation/Device interface for Respiratory Products
Physics Based Modeling

- Pharmaceutical formulation
  - Analyzing process equipment (mixing, heat generation, drying etc).
  - Evaluating product performances (dissolution, spray pattern etc).

- Formulation/Device interface
  - Optimize drug/device interface
  - Device patient interface

- Process scale up
Formulation/Device interface for Respiratory Products

- Optimize drug/device interface
  - Capsule based passive DPI (CFD)
  - Mist (CFD)

- Device patient interface
  - MDI vs DPI (CFD)
  - MDI with and without holding chamber (CFD)
  - Particle growth in the airway (CFD)
Pulmonary Drug Delivery

Formulation

MDI
Nebulizer
DPI

Device

Propellant
Powder Reservoir (eg, Turbuhaler)
Blisters disk (eg, Rotadisk)
Blisters strip (eg, Diskus)
Capsule (eg, Rotahaler)

Combination products

Extrathoracic Deposition (> 5µm)

Respirable particles (1-5 µm)

Undetached

Agglomerated particles
Inhaler Design: Simulation

- Physical properties
  - Aerodynamic diameter
  - Inter-particulate forces

Well accepted for DPIs

- Particle deposition in the lung/airways

Well accepted for upper airways (MT-TB)

- Aerodynamic properties
Inhaler Design

System description

Coding and simulation (Simulation tool)

Experiments (Device/formulation)
## Physics Based Models

<table>
<thead>
<tr>
<th>Inhalers</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPIs</td>
<td>Airflow with the device Mousepiece geometry Particle-wall/ particle-particle collisions Powder emptying; capsule spinning Particle de-aggregation mechanism</td>
</tr>
<tr>
<td>MDIs</td>
<td>Aerosol plume behavior Nozzle diameter Propellant property Holding chamber</td>
</tr>
<tr>
<td>Nebulizers</td>
<td>Atomization mechanism; piezoelectric</td>
</tr>
</tbody>
</table>

Followed by drug deposition in the airways!

Particle Deposition in the Airways

Weibel human airway model: 0-23 generations

- Particle Diameter (m)
  - 6.0e-006
  - 5.0e-006
  - 4.0e-006
  - 3.0e-006
  - 2.0e-006
  - 1.0e-006
  - 9.0e-007

- Impaction
- Sedimentation

Alveoli (deep lung): 1-5 µm

Video of CFD simulations
Turbulence is a dominant airflow in a device and large airways which tend to produce chaotic vortices.
Turbulence Simulation (CFD)

- **Direct numerical simulations (DNS)**
  Resolve all eddies (meshes)

- **Large eddy simulation (LES)**
  Intermediate approach

- **Reynolds-averaged navier-stokes (RANs)**
  Model just ensemble statistics
  Most common method in DPI simulation
Device/Formulation Interface
Case study I: DPI (CFD)

Capsule Based Passive DPI

DPI details
- Formulation: spray-dried sub-micrometre particle agglomerates
- Mouse-piece with built in 3D rod array
- Optimized for sub-micrometre particle dispersion

Physics-based modeling with *in vitro* validation
- Mouthpiece geometry and airflow
- Particle-wall/ particle-particle collisions
- Particle de-aggregation mechanism
- Powder emptying; capsule spinning, size of the capsule
- Drug deposition in Mouth-Throat (MT) region

Y-J. Son et al., Pharm. Res. 30 (2013)
S.R.B. Behara et al., Pharm. Res. 31 (2014)
Case study I: Simulation (MP Design)

Y-J. Son et al., Pharm. Res. 30 (2013)
Case study I: Validation

Key Turbulence Factor Simulated

<table>
<thead>
<tr>
<th>Inhaler</th>
<th>k</th>
<th>TI</th>
<th>ω</th>
<th>NDSD</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.2</td>
<td>13.5</td>
<td>61.9</td>
<td>82.6</td>
<td>6</td>
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<tr>
<td>2</td>
<td>5.6</td>
<td>20.1</td>
<td>111.3</td>
<td>148.4</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>12.1</td>
<td>47.2</td>
<td>64.85</td>
<td>86.5</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>474.2</td>
<td>50.5</td>
<td>132.87</td>
<td>106.3</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>9.5</td>
<td>38.3</td>
<td>72.67</td>
<td>96.9</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>19.1</td>
<td>26.3</td>
<td>127.28</td>
<td>169.7</td>
<td>1</td>
</tr>
</tbody>
</table>

Experimental Results

<table>
<thead>
<tr>
<th>MMD (µm)</th>
<th>FPF$_{1µm/ED}$</th>
<th>FPF$_{5µm/ED}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.35</td>
<td>18.8</td>
<td>89.5</td>
</tr>
<tr>
<td>1.21</td>
<td>26.8</td>
<td>95.8</td>
</tr>
<tr>
<td>1.36</td>
<td>19.2</td>
<td>94.5</td>
</tr>
<tr>
<td>1.27</td>
<td>26.9</td>
<td>95.9</td>
</tr>
<tr>
<td>1.31</td>
<td>20.4</td>
<td>95.5</td>
</tr>
<tr>
<td>0.98</td>
<td>38.8</td>
<td>94.6</td>
</tr>
</tbody>
</table>

$k$: turbulence kinetic energy  
$TI$: turbulence intensity  
$ω$: specific dissipation rate  
NDSD: non-dimensional specific dissipation rate

$k = turbulence kinetic energy$  
$TI = turbulence intensity$  
$ω = specific dissipation rate$  
NDSD: non-dimensional specific dissipation rate

$NDSD = \bar{\omega} \cdot t_{exp}$

$t_{exp} = \frac{V}{Q}$

Y-J. Son et al., Pharm. Res. 30 (2013)
Case study 2: Respimat (CFD-Visualization)

Respimat Soft Mist (Boehringer Ingelheim)

- New liquid aerosol generating device.
- Two high-velocity jets created at the uniblock outlets and generate a slow-moving aerosol.
- The velocity is approximately 0.8 m/s at 10 cm distance from the nozzle, compared with 2.0-8.4 m/s for a conventional pMDI.

Influencing factors (CFD simulation):
- Jet velocity
- Impaction angle
- Solvent
- MP design (air-flow in the MP)

H. Wachtel et al., RDD (2008).
Case study 2: Respimat (Impinging Jets)

MP Design: CFD and Flow Visualization

- The larger air vents incorporated in the marketed Respimat design (b) minimize the back-flow.
- CFD calculations provide numerical data but require careful selection of the mathematical models of turbulent flow.
- The uncertainty surrounding model selection can be avoided by utilizing flow visualization studies using up-scaled inhaler models.
Device/Patient Interface Optimization
Case Study 4: DPI vs. MDI Lung Delivery

- Drug deposition in MT-TB region

<table>
<thead>
<tr>
<th>Product</th>
<th>Device</th>
<th>API</th>
<th>Aerosolization</th>
<th>Correct use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flovent HFA (GSK)</td>
<td>MDI</td>
<td>Fluticasone (44µg)</td>
<td>Turbulence and compressible flow</td>
<td>Slowly Deeply (SD)</td>
</tr>
<tr>
<td>Flovent Diskus (GSK)</td>
<td>DPI</td>
<td>Fluticasone (50µg)</td>
<td>Turbulence and high speed jet</td>
<td>Quickly Deeply (QD)</td>
</tr>
</tbody>
</table>

- CFD and Experimental Validation

<table>
<thead>
<tr>
<th>Tests</th>
<th>Flow profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct MDI</td>
<td>SD</td>
</tr>
<tr>
<td>Correct DPI</td>
<td>QD</td>
</tr>
<tr>
<td>Incorrect MDI</td>
<td>QD</td>
</tr>
<tr>
<td>Incorrect DPI</td>
<td>SD</td>
</tr>
</tbody>
</table>

P.W. Lonest et al., Pharm. Res. 29 (2012)
Case Study 3: DPI vs. MDI Lung Delivery

- Used a well validate model
- With “correct” inhalation, MDI delivers 2x dose to the upper TB with \( \frac{1}{2} \) the loss in the MT
- DPI was not influenced by inhalation pattern
- CFD is a useful tool to optimize device/patient interface.

<table>
<thead>
<tr>
<th></th>
<th>DPI</th>
<th>MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFD</td>
<td>65.2%</td>
<td>44.3%</td>
</tr>
<tr>
<td>Experimental</td>
<td>72.5%</td>
<td>39.0%</td>
</tr>
</tbody>
</table>
Case Study 4: MDI With/Without Holding Spacer

Proventil HFA (Merck)

Proventil HFA/Holding Spacer

- Validation can be done using published data
- Help design medical devices with improved drug delivery efficacy.

Influence of Humidity in the Airways

- CFD predictions of excipient effect on exiting growth size for an aerosol.
  - Initial size: 0.9 µm
  - Albuterol sulfate (AS), AS with citric acid (CA) and AS with NaCl
  - Spray dried AS with Mannitol (MN) and L-Leucine (Leu)

Y-J. Son et al., European J Pharm. Sci 49 (2013)
Case Study 5: Particle Behaviors in the Airways

- CFD predictions of growth for insulin : NaCl (50:50 w/w) combination particles for slow and deep inhalation
Limitations in Computational Simulation

- Highly complex nature of aerosol formation and transport complicates the application of computational methods in inhaler design.
  - Difficult to capture all the relevant physics involved in inhaler operation.
  - Difficult to simulate the entire process (e.g., MDI spray physics, metering etc.).
  - Simplifications should be justified with some degree of validation.

- Complexity of variations in respiratory tract geometry is associated with additional factors such as breathing pattern, age, disease state and patient-device interaction.
  - Drug deposition will be influenced by airways geometry.
  - Limitation in simulations in deep lung drug deposition due to the alveolar regions that contract and expand with time.
  - Current in vivo simulation is limited to upper airways.
Summary

- Physics-based modeling can provide an effective tool for analysis.

- Physics based modeling is well established for
  - Dry powder inhaler; turbulence mechanism (CFD)
  - Drug deposition in upper airways (MT-TB).

- CFD is not meant to wholly replace traditional experimental techniques but rather to provide an additional means for analysis.

- Regulators have yet to approve significant changes to inhalers using combinations of computational and experimental methods.
Backup
Particle De-agglomeration

- **Particle de-agglomeration in DPIs**
  - Need to understand a break-up energy.
  - Turbulence is not the only energy source!!

- **Discrete element modeling (DEM)**
  - Useful to understand the exact mechanism of aerosolization and particle de-agglomeration in these systems.
  - Coupling CFD methodology to DEM may provide a means to predict the process as a whole.

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**Discrete particle system**

Specify interactions between two bodies

Integrate the equations of motions for all particles
Computational Simulation

- Physical equations are solved in 3D geometry
  - Realistic geometries need to be constructed
  - Simulation process subdivided geometry into small discrete volumes (mesh or grid).

- Concurrent experiments-computational simulation should be conducted to leverage the strengths of each approach

**Experiments**
- Provide initial size distribution of the aerosol
- Benchmark deposition within a realistic airway model
- Used to initially validate modeling results

**Simulation**
- Allows modification and optimization of device performance
- Analyze experimentally difficult systems (entire TB or alveolar airways) and provide additional resolution of deposition
Particle Deagglomeration Mechanism in DPIs

<table>
<thead>
<tr>
<th>Passive</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Narrow passage: Easyhaler®, AIR®</td>
<td>• Battery powered: Spiros®</td>
</tr>
<tr>
<td>• Impaction: Aerolizer®</td>
<td>• Pressured air: Exubera®, Aspirair®</td>
</tr>
<tr>
<td>• Tortuous and helical channel: Turbuhaler®</td>
<td>• Piezo-electric: Microdose®</td>
</tr>
<tr>
<td>• Air classifier: Airmax®, Novolizer®</td>
<td>• In-situ micronization: MAGhaler®</td>
</tr>
<tr>
<td>• Cyclone: 3M Conix™</td>
<td>• Spring impactor and tape: 3M Taper™</td>
</tr>
</tbody>
</table>

- Majority of marketed DPIs adopt a passive mechanism
- Compared with pMDIs and nebulizers, CFD has been used to a larger extent in the analysis of DPIs.
- Due to the strong dependence of DPI performance (passive) on airflow

Case study 2: DPI (CFD-DEM Coupling)

Particle trajectories in the device

- The powder dispersion in a cyclonic flow was simulated
- Model device: Aerolizer® (Novartis)

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>D50 (µm)</td>
<td>4.1</td>
<td>3.3</td>
<td>3.3</td>
<td>3.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Span</td>
<td>0.4</td>
<td>0.4</td>
<td>0.9</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Diameter (µm)</td>
<td>50.4</td>
<td>51.1</td>
<td>51.1</td>
<td>51.4</td>
<td>52.8</td>
</tr>
<tr>
<td>Strength (pa)</td>
<td>416.5</td>
<td>527.1</td>
<td>590.9</td>
<td>622.5</td>
<td>755.5</td>
</tr>
</tbody>
</table>

Z.B Tong et al., Chemical Engineering Journal 164 (2010).
Case study 2: DPI (Particle Trajectories)

Particle size
- 2.6, 3.3, 4.6 µm
- Smaller the particles size, lesser the particle breakup

Size is a more clinical factor

Polydispersity
- 0.4, 0.9, 1.2
- Smaller the span, better the particle breakup

Z.B Tong et al., Chemical Engineering Journal 164 (2010).
Computational Simulation

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